Please add the following new claim:

Claim 23. (New) A method according to claim 10 wherein the mammal is a human.

Remarks

In an Office Action mailed July 31, 2001, claims 1 - 10, 12 - 15, and 22 are pending and all claims stand rejected. Claim 3 has been cancelled. Claim 10 has been amended to clarify the language. Applicants assert that the amendment to claim 10 does not narrow the claim in any manner. Claim 23 has been added. Support for claim 23 is provided in the specification at page 4. Applicants have not raised any issues of new matter. Claims 1, 2, 4 - 10, 12 - 15, 22 and 23 are currently pending.

Objection to the Specification

The Examiner has indicated that Applicants have attempted to incorporate essential subject matter from foreign applications. Applicants traverse this objection. The publications incorporated by reference do not contain essential material. Therefore, the Examiner's position is not correct. The incorporation by reference is entirely proper. Applicants assert that a detailed explanation of their synthesis is not essential to make the present invention, because a skilled artisan would know the structure and the synthesis of each compound. More importantly, the individual preparation of the compounds is not the inventive step of the present invention. The present invention utilizes well known compounds in a novel and non-obvious combination. The synthesis of the identified compounds are well known in the art, and a skilled artisan would not suffer an undue burden of experimentation in obtaining the components of the claimed combination.

35 U.S.C. §112, second paragraph rejection

Claims 10 and 12 - 15 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite because the claim recites "a mammal" and also recites "including a human". Claim 10 has been amended for clarification to recite "a mammal" and new

dependent claim 23 recites "a human". Applicants respectfully submit that the rejection has been overcome and request withdrawal of the rejection of claims 10 and 12 - 15 under 35 U.S.C. §112.

35 U.S.C. §103 (a) rejection

Claims 1 - 10 , 12 - 15, and 22 are rejected under 35 U.S.C. §103 as *prima facie* obvious over Korba and Glazier. Applicant respectfully traverse the rejection. To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), three criteria must be met: 1) there must be some suggestion or motivation in the references themselves to make the claimed combination or modification; 2) there must be a reasonable expectation of success; and 3) the references must teach or suggest all the claimed limitations. MPEP § 2142.

None of the cited references specifically teach the use of the claimed combination of (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one (lamivudine) or a pharmaceutically acceptable derivative thereof and a second therapeutic agent, bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl] adenine (adefovir dipivoxil) or adefovir or a pharmaceutically acceptable derivative thereof for the treatment of HBV infection. The Examiner states that, "The prior art does not expressly disclose that the employment of lamivudine in combination with adefovir or adefovir dipivoxil is useful in a pharmaceutical composition or formulation and methods of treatment of HBV infections." Korba et al teaches lamivudine for the treatment of HBV infections. Glazier teaches adefovir or adefovir dipivoxil for the treatment of HBV infections. Nowhere in the Korba reference is it taught or suggested that lamivudine can be used in combination with the claimed compositions containing adefovir or adefovir dipivoxil.

Glazier does not teach that adefovir dipivoxil can be used in combination with other antiviral agents to treat HBV infections.

Korba teaches that lamivudine may be used in combination with interferon or penciclovir, an anti-herpes agent, for the treatment of HBV infections, but does not

teach the claimed combination and provides no motivation for the combination of the present invention.

> [I]dentification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the *specific* combination that was made by the applicant (emphasis added). *In re Kotzab*, 2000 WL 892795 (Fed. Cir. 2000).

Furthermore "obvious to try" is not the correct standard under § 103(a).

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of errors. In some cases, what would have been "obvious to try" would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *In re O'Farrell*, 853 F.2d 894, 903, U.S.P.Q. 2d 1673 (Fed. Cir. 1988).

The determination of whether a combination of drugs directed against a single target will interact in a synergistic, additive or antagonistic manner is still an experimental science. It is difficult, if not impossible, to predict which combinations of drugs will provide a beneficial result and those that may be clinically problematic (Merrill, D.P et al. , *Journal of Infectious Diseases* 1997, Vol. 176, No. 1, p. 265-8).

Because Korba and Glazier, either alone or in combination, do not teach the present invention, do not provide a motivation to make the claimed invention, and do not provide a reasonable expectation of success, Applicants respectfully submit that Examiner's rejection of the claimed combination of (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and adefovir or adefovir dipivoxil for the treatment of HBV infections is not a proper *prima facie* case under 35 U.S.C. § 103, but is instead an improper rejection based on an "obvious to try" standard.

Moreover, the specification demonstrates the claimed combination of (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one and adefovir shows unexpected, synergistic activity against HBV production. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness." MPEP § 716.02(a).

Figure 1 of the specification represents an isobologram indicating that the combination of lamivudine and adefovir exerts a synergistic effect *in vitro* in the inhibition of HBV replication. "All rational definitions agree that synergism occurs where the joint action of two agents is greater than that expected from the action of each agent acting alone." (Harvey, R.J., , *Reviews of Infectious Diseases*, 1982, Vol. 4, No. 2, p. 255-260). The demonstration of the synergistic effect of the combination of lamivudine and adefovir dipovoxil is the demonstration of an unexpected effect. Therefore, since the combination of the present invention produces synergistic results, it is not obvious in view of Korba and Glazier alone or in combination. Applicants respectfully requests withdrawal of the rejection of claims 1 - 10, 12 - 15 and 22 under 35 U.S.C. § 103(a).

In view of the amendment and foregoing discussion, it is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted,

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Claim Version with Markings to Show Changes Made

Claim 3 (Cancelled).

Claim 10. (Amended) A method for the treatment of a mammal[, including a human,] with an HBV infection comprising administration of a therapeutically effective amount of a combination comprising (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-pyrimidin-2-one or a pharmaceutically acceptable derivative thereof and a second therapeutic agent selected from (9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof, and bis(pivaloyloxymethyl)(9-[(R)-2-(phosphonomethoxy)ethyl]adenine or a pharmaceutically acceptable derivative thereof.

Claim 23. (New) A method according to claim 10 wherein the mammal is a human.